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‘Mitochondrial replacement techniques: who are the potential users and will they benefit?’ in *Bioethics* (under press).

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Abstract

In February 2015 the UK became the first country to legalise high-profile mitochondrial replacement techniques (MRTs), which involve the creation of offspring using genetic material from three individuals. The aim of these new cell reconstruction techniques is to prevent the transmission of maternally inherited mitochondrial disorders to biological offspring. During the UK debates, MRTs were often positioned as a straightforward and unique solution for the ‘eradication’ of mitochondrial disorders, enabling hundreds of women to have a healthy, biologically-related child. However, many questions regarding future applications and potential users remain. Drawing on a current qualitative study on reproductive choices in the context of mitochondrial disorders, this paper illustrates how the potential limitations of MRTs have been obscured in public debates by contrasting the claims made about the future beneficiaries with insights from families affected by mitochondrial disorders and medical experts. The analysis illuminates the complex choices with which families and individuals affected by mitochondrial disorders are faced, which have thus far remained invisible. An argument is presented for improved information for the public as well as an intensification of critical empirical research around the complex and specific needs of future beneficiaries of new reproductive biotechnologies.

Introduction

In February 2015 the UK became the first country to legalise high-profile mitochondrial replacement techniques (MRTs)¹, which aim to prevent the transmission of inherited disorders by creating offspring using genetic material from three individuals. During the UK public and parliamentary debates, MRTs were often positioned as a straightforward and unique solution for the ‘eradication’ of mitochondrial disorders, enabling hundreds of women to have a healthy, biologically-related child. However, many questions regarding the future applications and potential users remain.

Drawing on a current qualitative study on reproductive choices in the context of mitochondrial disorders, this paper discusses the issue of the future beneficiaries of MRTs by contrasting public and media discourses surrounding the techniques with the insights of families directly affected by mitochondrial disorders, as well as medical experts. The paper suggests that while the media interest in these techniques and the surrounding debates have certainly increased the visibility of mitochondrial disorders and resulted in public interest in them, the discussions of the technologies were at times sensationalist and misleading with respect to their potential application. These public debates have obscured the potential different limitations of MRTs. Moreover, these discourses represented families affected by mitochondrial disorders in ways that ignored the specific difficulties they face and the complex choices they have to make in order to have a child.

The paper begins with an overview of the medical specificities of mitochondrial disorders and their impact in terms of reproductive choices, followed by a brief description of the study on which the paper is based. By examining key documents of the UK debates on MRTs and their media coverage, I then highlight the lack of discussion of the potential future users of the techniques and show how families affected by mitochondrial disorders have mainly been described as a homogenous group in need of MRTs to have healthy, biologically related children. In the final section, I attempt to provide a better understanding of the complex choices with which families and individuals affected by mitochondrial disorders are faced, by drawing on empirical data to consider the medical, legal, individual and financial constraints limiting the future potential use of MRTs. I conclude by highlighting the importance of empirical research and improved information for the public, in order to consider the complex and specific needs of future beneficiaries of new reproductive biotechnologies.

Background

Mitochondrial disorders and reproductive choices

MRTs are new cell reconstruction techniques aimed at preventing the transmission of maternally inherited mitochondrial disorders to biological offspring. These rare disorders are caused by dysfunctions of the mitochondria, the organelles situated in the cell cytoplasm

¹ Various terminologies have been used to designate these new reproductive technologies. I use the term ‘mitochondrial replacement techniques’ as it offers a relatively neutral description of the techniques, even though, strictly speaking, it is the whole cell cytoplasm which is replaced and not just the mitochondria.

which produce the energy for the cell². The more faulty mitochondria that are present in the cell, the more likely it is that defects will be created in the cell's energy production. This can cause severe and often life-threatening diseases (such as dementia, Melas, Pearson syndrome or myopathy), which particularly affect the organs requiring more energy (e.g. brain, liver, muscles and eyes). There is currently no treatment to cure these disorders and the evolution of various symptoms is very uncertain. They usually amplify with time however, possibly leading to death. While mitochondrial dysfunctions can result from mutations of the mitochondrial DNA, which is maternally inherited, it is important to keep in mind that many mitochondrial disorders are caused by nuclear DNA. Mitochondria's functioning is indeed governed both by the 37 mitochondrial genes and by hundreds of genes from the nucleus³.

Mitochondrial disorders have an important impact on reproduction, not only because they can affect the pregnancy but also because there is a risk of transmitting the disorders to future offspring. In such cases, reproductive decision-making is especially complex, as it is difficult to predict if a future child will develop disorders, the stage of life at which they will occur, and the extent of the symptoms. There are currently several possibilities for women at risk of transmitting the disorders, some of which are dependent on a genetic diagnosis, the mutation type and their individual mutation load⁴. These possibilities are: naturally conceiving a child with the risk of transmitting the disorder; adopting a child; using egg donation; using prenatal diagnosis (PND); or using preimplantation genetic diagnosis (PGD). Whilst some uncertainty remains with PGD or PND for maternally inherited disorders⁵, adoption and egg donation constitute safe options to avoid transmission.

Mitochondrial replacement techniques

To prevent the transmission of mitochondrial disorders to future offspring, two new techniques have been developed over the past 10 years in the US and UK. One of these techniques consists of transferring the nucleus of the affected mother's egg into a healthy enucleated donor egg. In other words, the nucleus of the donor egg is replaced by that of the intending mother. The newly reconstructed egg is then fertilised by the chosen sperm. This technique is called 'maternal spindle transfer'⁶. The transfer of the nucleus can also be done after fertilisation on an early embryo in the case of 'pronuclear transfer technique' (PNT). This procedure was initially developed in the UK by a research team at Newcastle University⁷.

The striking novelty in both cases is that the conceived child will inherit DNA from three individuals, not only the nuclear genome (which is thought to determine all unique individual characteristics and traits) from both intending parents, but also, albeit to a much lesser extent,

² Nuffield Council on Bioethics. 2012. *Novel Techniques for the Prevention of Mitochondrial DNA Disorders: An Ethical Review*. London: Nuffield Council on Bioethics.

³ P. F. Chinnery. Mitochondrial Disorders Overview. *GeneReviews* 2000 (updated 2014). Available at: <https://www.ncbi.nlm.nih.gov/books/NBK1224/>.

⁴ See below.

⁵ A. L. Bredenoord, G. Pennings & G. de Wert. Ooplasmic and Nuclear Transfer to Prevent Mitochondrial DNA Disorders: Conceptual and Normative Issues. *Human Reproduction Update* 2008; 14: 669–78.

⁶ M. Tachibana et al. Mitochondrial Gene Replacement in Primate Offspring and Embryonic Stem Cells. *Nature* 2009; 461: 367–72.

⁷ L. Craven et al. Pronuclear Transfer in Human Embryos to Prevent Transmission of Mitochondrial DNA Disease. *Nature* 2010; 465: 82–85.

the mitochondrial DNA from the egg donor (37 genes). Moreover, this donated mitochondrial DNA will be transmitted over the generations, through the maternal line.

Research aims and methods

The aim of the research on which this paper is based is to gain a better understanding of the interactions between scientific progress, policies and people's lives by exploring the issues raised by new MRTs⁸. It seeks to understand, in particular, the perceptions and experiences of women whose families are affected by mitochondrial disorders, especially regarding their reproductive options. The study included exploratory interviews with genetic counsellors, clinicians and support group representatives, as well as in-depth interviews with 28 women affected by mitochondrial disorders⁹, either because they had the disease (n~9) or because their children were affected by the disorder (n~19). These women were recruited between 2014 and 2016 through a major UK support group, two NHS Trusts and snowballing. 14 were interviewed on their own and 14 with their partner or their mother¹⁰.

The analysis presented in this paper is based on data collected in interviews with women affected by mitochondrial disorders pertaining to their specific family context and medical condition¹¹, as well as from discussions with medical experts¹². It also draws on the analysis of key textual documents (i.e. media releases, public reports, parliamentary documents and informative documentation circulated by various stakeholders during the debate), as well as the observation of numerous public and parliamentary debates surrounding MRTs which took place between 2013 and 2015.

The potential beneficiaries and future applications of MRTs in public debates

While research on MRTs has been ongoing for more than 10 years in the UK, public discussions of the techniques and their related issues only really began after the UK research team announced the first successful application of PNT to a human embryo in 2010¹³. This prompted the question of the possible legalisation of the technique for treatment. A licence had been granted in 2005 to the Newcastle research team to experiment with PNT for research, but the technique was still banned for treatment applications in the UK¹⁴, as in most countries, because it involves germline modifications¹⁵.

⁸ For more information on the MitoFamily Study, see: <http://www.dmu.ac.uk/research/research-faculties-and-institutes/health-and-life-sciences/reproduction-research-group/the-mitofamily-study.aspx>.

⁹ At the time of the publication of this paper.

¹⁰ Given the sensitivity of the topic, participants were given the possibility to choose which option suited them best.

¹¹ Rather than the data pertaining to their experiences of living with the disease more generally and their perceptions of the techniques. Further publications to follow will address (in more detail) the empirical gap relating to the women's lives.

¹² Data from the 'context setting' interviews with key experts in the field informed the content of the paper and helped identify key textual sources. However, direct quotes from the experts are not used as these interviews focused primarily on the technical aspects of MRTs.

¹³ Craven et al., *op. cit.* note 7.

¹⁴ HFEA. 1990. *Human Fertilisation and Embryology Act 1990, as amended 2008*.

¹⁵ Germline modifications refer to genetic changes in the gametes or the early embryo that will be passed on to subsequent generations.

In this context, a number of initiatives were taken by the Government and science-based organisations in order to assess the safety of MRTs and discuss their ethical issues, including the publication of a report by a specific working group of the Nuffield Council on Bioethics (NCB)¹⁶, the launch of a public consultation by the Human Fertilisation & Embryology Authority (HFEA)¹⁷ and the commissioning of a scientific review of the safety and efficacy of MRTs by the HFEA. Several public events were also organised on the topic¹⁸. Besides safety issues, the academic and public discussions surrounding MRTs mainly focused at that stage on four ethical issues¹⁹: the relevance of defining and treating MRTs as germline therapies; the social and psychological impacts of having a genetic connection to three persons; the legal status of the mitochondrial donors; and the possibility of initially treating only male embryos to avoid passing on possible unforeseen side effects (due to the fact that mitochondrial DNA is passed on to the embryo and subsequent generations through the maternal line).

While the abovementioned reports often explained the objective and the functioning of MRTs and briefly described what mitochondrial disorders could be, there were, however, very few details of the potential beneficiaries targeted by MRTs. These were usually referred to as ‘patients’, ‘women carrying maternal disorders’, ‘women with mitochondrial disorders’ or ‘women who would otherwise pass on mutated mitochondria through their eggs’, but these broad descriptions did not provide a sense of the characteristics and the number of women that could possibly benefit from the techniques. Only approximate epidemiological rates, such as ‘one in 200 babies with mitochondrial disorders born per year in the UK’²⁰, were regularly mentioned, implying that this would be the number of potential ‘lives’ which could be saved by the techniques. The reports also regularly made reference both to ‘the families affected by mitochondrial disorders’ and to ‘the women who could benefit from the techniques’ without clearly differentiating them, which tended to assimilate these two groups that are in practice very distinct (see below). Moreover, it was difficult to know from the debates and the reports what patients’ views and experiences were in terms of reproductive choices. The individuals whose families were affected by mitochondrial disorders and who replied to the HFEA consultation or the call for evidence from the NCB seemed very favourably disposed towards these techniques²¹. However, their numbers were very low²² and it was difficult to ascertain whether they themselves could use the techniques.

The HFEA public consultation was accompanied by a number of press releases discussing the possible legalisation of MRTs and some of its safety and ethical issues, often persistently

¹⁶ Nuffield Council on Bioethics, *op. cit.* note 2.

¹⁷ Human Fertilisation and Embryology Authority. March 2013. *Mitochondria Replacement Consultation: Advice to Government*.

¹⁸ Besides two public meetings held by the HFEA, there were also six debates organised by science-based organisations and research groups between September and December 2012, mostly in London.

¹⁹ Nuffield Council on Bioethics, *op. cit.* note 2; Bredenoord, Pennings, and de Wert, *op. cit.* note 5.

²⁰ This number was regularly reported in the press without specifying that it is an estimation of the children presenting various mutant loads, the majority of them developing either no symptoms or only mild ones. It is estimated that one in 6,500 children develop a more severe mitochondrial disorder (Nuffield Council on Bioethics, *op. cit.* note 2, p.24).

²¹ *Ibid*: 88.

²² For instance, one patient focus group was organised by the HFEA in December 2012 to explore in-depth views on MRTs. This involved only six participants, some of them being parents of children affected by nuclear defects and who therefore could not use MRTs themselves (HFEA, *op. cit.* note 13, p.7–8).

highlighting the fact that MRTs would create ‘three-parent babies’²³. The potential users of the techniques and patients with mitochondrial disorders were rarely mentioned. When this was the case, journalists usually referred to the dramatic case of Sharon Bernadi, a mother who had lost several children to mitochondrial disorders and whose story represented the culmination of desperation and suffering associated with mitochondrial disease²⁴.

Following the HFEA’s advice to permit the techniques, a consultation on draft regulations to allow such treatments to be carried out was launched by the Department of Health in March 2014. From that point, discussions of the ethical issues mentioned above diminished considerably. The draft regulations echoed the recommendations provided by the HFEA on the different ethical issues²⁵, which no longer seemed to be discussed the following year. As the parliamentary debates approached, complex ethical discussions were progressively replaced by sharper confrontations of pro and con arguments, calling upon either strong emotional imaginaries or complicated techno-scientific arguments.

On the one hand, the opponents of MRTs argued that the techniques were unsafe and unpredictable. For instance, Robert Ffello MP explained that ‘based on the available data, [...] we cannot rule out the possibility that these techniques could cause the people born as a result to have illnesses or disabilities. The Government have a responsibility, as we all do, to avoid such eventualities, and we cannot take that lightly. We might not know the result for many generations. We might not know whether some damage has been caused until three, four or five generations later. We simply cannot know that’²⁶. In particular, there were also very long and controversial discussions about the possible impact of ‘mismatching’ nuclear and mitochondrial DNA and the ‘potentially serious and unpredictable consequences’ this could have on future offspring, after biologist Ted Morrow suggested that ‘more experiments needed to be undertaken on species more closely related to humans to understand these possible damaging effects’²⁷. Another main argument against MRTs was that they represented a eugenic threat by enabling ‘human genetic modifications’ and a slippery slope that could lead to ‘a designer baby market’²⁸. For instance, Fiona Bruce MP claimed that ‘this [was] a case of genetic engineering’ and warned that ‘once this alteration has taken place and once the genie is out of the bottle, and once these procedures that we are being asked to authorise today go ahead, there will be no going back for society, and certainly not for the individuals concerned’²⁹. These claims were often reported in the media in a sensationalist way³⁰.

²³ N. Collins. 2012. Babies with Three Parents Possible within Three Years. *Telegraph* 19 January 2012. Available at: <http://www.telegraph.co.uk/news/science/science-news/9025121/Babies-with-three-parents-possible-within-three-years.html>.

²⁴ M. Henderson. 2010. Babies with Three Parents May Be Key to Preventing Genetic Disorders. *The Times (London)* 14 April 2010. Available at: <http://www.thetimes.co.uk/tto/science/genetics/article2477217.ece>; R. Dicker. 2012. Sharon Bernadi Loses 7 Children to Leigh’s Disease - but Hopes for Cure. *The Huffington Post*, 20 September 2012. Available at: http://www.huffingtonpost.com/2012/09/20/sharon-bernardi_n_1900248.html.

²⁵ Human Fertilisation and Embryology Authority, *op. cit.* note 13.

²⁶ Hansard. 2014. House of Commons Debates. 01 Sep 2014, col 105.

²⁷ T. Morrow. 2014. Safety Concerns Remain over Three-Person IVF. *The Guardian* 22 July 2014. Available at: <https://www.theguardian.com/science/2014/jul/22/three-person-ivf-mitochondria-dna>.

²⁸ D. King. 2012. Human Genetic Engineering on the Doorstep The Threat of ‘mitochondrial Replacement’ Techniques. Human Genetics Alert. Available at: <http://www.hgalert.org/Mitochondria%20briefing.pdf>.

²⁹ Hansard. 2015. House of Commons Debates. 03 Feb 2015: 18.

³⁰ S. Knapton. 2014. Government Accused of ‘GM Baby’ Cover-Up. *Telegraph* 28 July 2014. Available at:

On the other hand, stakeholders in favour of MRTs increasingly focused their argument on the suffering of families and the claim that the techniques would enable them to have healthy biological children and, in the longer term, eradicate the disorders. For instance, Luciana Berger MP, during the debate at the House of Commons, stressed that ‘we have within our reach the possibility of eradicating mitochondrial disease from families who have been blighted by it for generations: families who have endured a disease for which there is no cure, who have suffered daily battles with painfully debilitating symptoms, and who have sadly lost their children prematurely’³¹. These arguments were often accompanied by moving and tragic stories of families affected by the disorders, which were provided and put forward by patient associations and parent advocates. For example, Alex Cunningham MP described at length the heart-breaking case of baby Jessica, who ‘will not live much longer—perhaps only a year or two. She cannot be fed naturally and relies on a feeding tube. Her body will not develop, which means that she will not grow and her internal organs will deteriorate. [...] If we are to avoid this horrific suffering in the future, we need the regulations now to make the necessary progress and help ensure that we do not have more babies like Jessica’³². These stories were also very prevalent in the media, where a number of people whose families were affected by mitochondrial disorders affirmed their support for the legalisation of the techniques³³. However, these descriptions were highlighting the need to prevent mitochondrial disorders, rather than providing information regarding who exactly could use MRTs and under which conditions.

This mobilisation of human suffering towards political projects constituted a good illustration of what Buchbinder and Timmermans have termed ‘affective economies’³⁴. These authors have highlighted the specific function of ‘affect’, which operates socially by resonating with and reinforcing broadly felt public sentiments and widely accessible emotions such as fear, anxieties and compassion, particularly where children’s lives are at stake. As the authors explain, this type of argument is not only efficient but also very difficult to criticise, as it foregrounds ‘morally valued activities’³⁵. The claim of the suffering of the patients was also constantly articulated in relation to a ‘rhetoric of hope’³⁶ based on the assumption that MRTs would be *the* technique that would solve patients’ reproductive problems. For example, during the debate at the House of Commons, Paul Burstow MP declared that MRTs are

<http://www.telegraph.co.uk/news/science/science-news/10995827/Government-accused-of-GM-baby-cover-up.html>; S. Connor. 2014. Exclusive: The Three-Parent Baby Trap - Is New IVF Technique Safe? *The Independent* 16 November 2014. Available at: <http://www.independent.co.uk/news/science/exclusive-the-three-parent-baby-trap-is-new-ivf-technique-safe-9864156.html>.

³¹ Hansard. 2015. House of Commons Debates. 03 Feb 2015: 14.

³² Hansard. 2014. House of Commons Debates 01 Sep 2014. Col. 108.

³³ R. McKie. 2014. Families Hope ‘Frankenstein Science’ Lobby Will Not Stop Gene Cure for Mitochondrial Disease. *The Guardian* 15 February 2014. Available at: <http://www.theguardian.com/science/2014/feb/15/mitochondrial-disease-gene-cure-ivf>; J. Gallagher. 2014. Three-person baby details announced. *BBC News* 27 February 2014. Available at: <http://www.bbc.co.uk/news/health-26367220>.

³⁴ M. Buchbinder & S. Timmermans. Affective Economies and the Politics of Saving Babies’ Lives. *Public Culture* 2014; 26.

³⁵ Ibid: 104.

³⁶ M. Mulkay. Rhetorics of Hope and Fear in the Great Embryo Debate. *Social Studies of Science* 1993; 23: 721–42.

‘about light at the end of the tunnel for thousands of families in this country. It is about the prospect of life lived, life realised, and about the potential opportunity to live’³⁷.

During the year preceding the parliamentary vote, more details were given regarding the number of women who could potentially use the techniques. The consultation document produced by the Department of Health in February 2014 indicated that MRTs ‘could apply to up to 10 cases per year initially’³⁸. This information was exaggerated in the press, with some newspapers reporting that ‘100 babies a year in the UK will have three parents’³⁹. One year later, the research team at Newcastle working on mitochondrial donation provided an estimation of the number of women aged between 15 and 44 who could potentially benefit from the techniques. This was based on an extrapolation of the prevalence of mtDNA mutations in North East England to the UK population and the fertility rate amongst these women. Their conclusion was that MRTs could enable ‘about 150 births a year *if all women opted for the procedure*’ (emphasis added)⁴⁰. The following day, BBC News announced that ‘nearly 2,500 women in the UK would benefit from a fertility technique to make babies from three people’⁴¹. During the parliamentary debate, it was also said that ‘there are potential benefits for the about 2,500 families affected by mitochondrial disease up and down this nation’⁴².

In retrospect, it is striking to observe how the scope and the characteristics of the women targeted by MRTs, when mentioned at all, have remained vague and confusing, both in media coverage and in public and parliamentary discussions. There was a conflation of all families affected by mitochondrial disorders and the women who could use MRTs. Moreover, little information was provided about the medical condition and family situation of the latter and about whether they themselves would be willing to use the techniques. In this respect, the information provided to the public did not provide either sufficient information about the application of the techniques or an in-depth understanding of patients’ views. It was often implied that any women who were affected by mitochondrial disorders, or whose families were, could benefit and would be willing to seek these benefits. This assumption also reinforced the injunctions not only to have a child, but specifically to have a biologically-related child, by whatever means required.

It is also worth noticing that bioethics and scientific discourses have dominated the debates and there has been a lack of detailed and empirical data from social sciences on these issues. Yet, as I suggest in the following section, the debate would have benefited from this kind of insight and from improved information on the specificities of MRTs.

³⁷ Hansard. 2015. House of Commons Debates 03 Feb 2015: 33 (MP Paul Burstow).

³⁸ Department of Health. February 2014. *Mitochondrial Donation. A Consultation on Draft Regulations to Permit the Use of New Treatment Techniques to Prevent the Transmission of a Serious Mitochondrial Disease from Mother to Child*: 41.

³⁹ V. Woollaston. 2014. 100 Babies a Year in UK Will Have Three Parents: Births ‘as Early as 2015’ in World First. *Daily Mail Online* 27 February 2014. Available at: <http://www.dailymail.co.uk/sciencetech/article-2569438/Are-triple-parent-embryos-set-ahead-UK-Department-Health-debate-controversial-technique.html>.

⁴⁰ G. S. Gorman et al. Mitochondrial Donation — How Many Women Could Benefit? *New England Journal of Medicine* 2015; 372: 887.

⁴¹ J. Gallagher. 2015. Thousands ‘Need Three-Person Babies. *BBC News* 29 January 2015. Available at: <http://www.bbc.co.uk/news/health-31017999>.

⁴² Hansard. 2015. House of Commons Debates 03 Feb 2015: 20 (MP Andrew Miller).

The potential users of MRTs from an empirical perspective

As previously discussed, the question of whether MRTs could provide affected women with healthy children was not sufficiently addressed in the debates. In practice, the picture is much more complicated, as will now be illustrated through insights gained from empirical research on reproductive choices in the context of mitochondrial disorders. The following analysis demonstrates that there are various medical, legal, individual and financial constraints, which can limit the use of MRTs in practice.

1. Who will be suitable for MRTs?

There are significant biological and medical limits to the application of MRTs, which are related to the specific type of mutation carried by the individual. As mentioned earlier, mitochondrial disorders can be caused by mutations of the mitochondrial DNA, as well as by mutations of the *nuclear* DNA, which also controls the functioning of the mitochondria. However, MRTs only concern mitochondrial disorders that are maternally inherited. Although this was not mentioned in the public and parliamentary debates, it is important to highlight that most maternally inherited mitochondrial disorders only develop in adulthood (e.g. Melas or MERRF syndromes), whereas mitochondrial disorders which severely affect babies and children are caused in about 80% of cases by nuclear defects⁴³ which are inherited from both parents. This means that these techniques will not be accessible to most families who have already lost a child from mitochondrial disorders and who wish to have another one. Yet these tend to be the people who make up the membership of support groups such as the Lily Foundation, which was highly involved in the debate to support the legalisation of MRTs.

There is nonetheless a minority of children affected by maternally inherited disorders (e.g. specific types of Leigh's syndrome) whose mothers could benefit from these techniques. But they represent a very small number of cases. Their mothers are usually asymptomatic carriers with no family history of mitochondrial disorders⁴⁴. In my study, I interviewed three women in this situation. These women had been tested for mitochondrial mutations and all carried a low mutation load, which made them unlikely to be allowed to use MRTs, as MRTs are only accessible, at least for now, to women with a very high mutation load (see below). They have, however, the option, under certain conditions, to use pre-implantation genetic diagnostic (PGD) to select an embryo with a low mutation load. In this respect, it is important to add that even if MRTs were made available to these women, it would be unlikely that the mutation could be detected and its transmission prevented in advance *before they had a first child affected by the disorder*. This means that there will still be a number of children developing mitochondrial disorders in the future, even if MRTs are used on a larger scale.

In light of the considerations above, it appears that only a small proportion of the women whose families are affected by mitochondrial disorder will be suitable for MRTs in practice.

⁴³ HFEA. 2014. *Third Scientific Review of the Safety and Efficacy of Methods to Avoid Mitochondrial Disease through Assisted Conception. 2014 Update*: 12.

⁴⁴ Indeed, 'women with no noticeable symptoms and no family history of disease can produce eggs with a high load of abnormal mtDNA and vice-versa' (Parliamentary Office of Science & Technology; March 2013. *POSTnote 431: Preventing Mitochondrial Disease*. Houses of Parliament: 2).

From a medical perspective, these will be women who are already diagnosed with maternally inherited mitochondrial disorders or who have had a child or a relative diagnosed with such a disorder, but not most of the families who have had a child affected by the disease⁴⁵. When they mentioned that mitochondrial disorders could be caused by both types of mutations, the official reports failed to mention the proportions or characteristics of the respective groups affected. During the parliamentary debates, it was striking to observe that most MPs did not even seem aware of this crucial distinction between nuclear and mitochondrial mutations. For instance, when Luciana Berger MP, who had hosted a public debate on MRTs the day prior to the vote on the regulations, was asked whether ‘mitochondrial disease from the nuclear DNA will remain in our population even after this treatment is licensed’, she replied: ‘it is not something I have been made aware of, and it certainly has not come up in any of the discussions or debates that I have attended’⁴⁶. Given the importance of this distinction in terms of access to MRTs, it is especially surprising and worrying that it was not discussed sufficiently in the parliamentary debates.

Media reports and public debates have also contributed to confusion regarding the identity of the future beneficiaries of the techniques. While moving stories and strong declarations of support from women whose families were affected by mitochondrial disorders were regularly put forward, it was rarely specified whether their families were affected by nuclear or mitochondrial mutations and thus whether these techniques were of any practical use to them. Often, in fact, they were not suitable for MRTs.

2. Who will be entitled to use MRTs?

There are also important legal limitations to the application of these techniques. The 2015 UK law indicates the circumstances under which a patient may be authorised to use MRTs. Specifically, there needs to be (1) ‘a particular risk that any egg extracted from the ovaries of [the intending mother] may have a mitochondrion abnormality caused by mitochondrial DNA’, as well as (2) ‘a significant risk that a person with those abnormalities will have or develop serious mitochondrial disease’⁴⁷. In other words, the intending mother needs to carry a maternally inherited mutation and her eggs need to contain a significant proportion of abnormal mitochondria. Moreover, there has to be a high probability of the future offspring developing a severe condition.

Such conditions of access are complex and difficult to assess in practice, as the intending mother not only has to be aware that she is a carrier, but also needs to obtain a genetic diagnosis in order to understand the specificities of her mutation and its impact on her reproductive choices. As mentioned earlier, some of these women may be asymptomatic or have only mild symptoms of the disorders. They will thus only discover they can transmit the condition *after* giving birth to a first affected child. Again, this means that MRTs will not cure or eradicate mitochondrial disorders at the population level but only eliminate the transmission risk for a specific pregnancy.

⁴⁵ One might, therefore, wonder how the rest of the families, many of whom were involved in the debates and supported MRTs, feel about not being able to use them.

⁴⁶ Hansard. 2015. House of Commons Debates 03 Feb 2015: 17.

⁴⁷ HFEA. 2015. *The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015*.

Additional complications regarding access emerge since the risk of ‘having mitochondrial abnormality caused by mitochondrial DNA’ is also dependent on the ‘mutation load’, that is, the percentage of affected mitochondria in a given tissue. MRTs will initially only be accessible to women with very high mutation loads, as high mutation loads are generally indicative of higher risks of developing symptoms and transmitting the disorder, even though this may vary between individuals⁴⁸. For women with high mutation loads, MRTs may also be the only reproductive techniques available if they want an unaffected and biologically related child⁴⁹. It is not always possible, however, to determine the intending mother’s mutation load through basic tests. For instance, I met two women who were told they were at risk of transmitting a mitochondrial disorder after their mother or their child had been diagnosed, but their tissue samples (e.g. blood, saliva and urine) did not appear to contain the mutations. Only egg testing, which is an invasive procedure, could assess whether this was the case. All mutations can indeed be concentrated solely within their eggs and be transmitted to future offspring. For these women, only egg testing or PGD will be able to determine whether or not they present a mitochondrial abnormality. In such cases, it might therefore be easier and cheaper to undergo PGD alone rather than to use MRTs.

The second condition in UK law governing access to MRTs concerns the severity of the disorder, which is even more difficult to assess. The identification of a number of particular genetic conditions for which MRTs would be appropriate is not sufficient, as the symptoms and syndromes caused by mitochondrial disorders can be very diverse, even for the same mutation. They can include for instance brain damage, muscle weakness or hearing or visual loss. It is also very difficult to predict whether future children will be affected; – the way siblings are affected can vary significantly – in terms of the way their health condition will evolve and whether they will be severely affected.

For instance, one woman I interviewed had started to have difficulties walking and hearing. Her mother had died in her early fifties after her symptoms had progressively worsened. Neither the daughter nor the doctors knew how her own condition would evolve. What can therefore be considered ‘severe’? Does it have to be ‘life-threatening’? The criteria provided by the HFEA regulations and guidelines are quite vague, as they suggest a case-by-case approach based on supporting evidence, whereby the ‘Authority’s assessment of the seriousness will be made, where possible, based on the most severe symptoms that could be expected for a particular patient’s case’⁵⁰.

3. How many will engage with MRTs?

During the public and parliamentary debates, the assumption was often made that any women at risk of transmitting the disorders and eligible for the techniques would choose to make use of the technology. However, existing studies show that there are a range of ethical,

⁴⁸ It seems that health problems usually occur when there is more than 60% mutated mitochondria in a cell, even though this threshold may vary according to the type of mutation, the tissue and between individuals (Nuffield Council on Bioethics, *op. cit.* note 2, p.23).

⁴⁹ If their mutation loads are very high, especially in their eggs, PGD may be inappropriate, as it will be difficult to find and select embryos with a low mutation load.

⁵⁰ HFEA. 2015. Guidance Note 33: Mitochondrial Donation. 9 October 2015: 9. Available at: http://www.hfea.gov.uk/docs/Guidance_note_33_-_Mitochondrial_donation.pdf.

psychological, social and possibly financial difficulties associated with the use of reproductive technologies, especially in complicated situations marked by much uncertainty and ambivalence⁵¹. Using a reproductive technology is rarely a straightforward decision, and various considerations need to be explored when looking at reproductive choices. In my research, although most female participants were of child-bearing age, many of them told me that they were not willing or able to use MRTs for various reasons.

A first set of reasons was linked to a physical state or medical condition. Amongst the women who had maternally inherited disorders in my study, a number had already developed significant symptoms that would prevent them from carrying a child (e.g. using a wheelchair) or that made them feel too weak to raise one. Some participants were also afraid that their condition would worsen and did not know if they would still be able to take care of a child later on in life. Interestingly, these crucial elements have never been mentioned in the public debates surrounding MRTs. Not only were the implications of mitochondrial disorders on the future mother's health condition not mentioned, but it was rarely pointed out that the future mother could herself be ill or was likely to become ill.

A second set of reasons related to current 'social' or family situation (e.g. age, family, work or relationship). While these reasons may not be directly linked to mitochondrial disorders as such, they are still significant when assessing the number of women who would be interested in using MRTs. Some of the participants indeed reported that they were no longer, or not yet, in the right circumstances under which they wanted to have a child, for example because they had no partner or did not feel psychologically or materially ready. Four of the participants had already had their children, before or after being diagnosed, and were not willing to have more. Having another child was also difficult to consider when taking care of a severely ill child or parent, which was the case for 11 of the 28 female participants in this study.

Beyond these social or relational reasons, there were also other significant concerns that prevented these women from being willing to use MRTs. For instance, an important issue for several interviewees was reluctant attitudes towards new reproductive and genetic techniques. Some thought the techniques were 'too complicated'. They therefore preferred to conceive a child 'naturally', i.e. without any medical assistance, - and to take the risk of transmitting the disorders or not to have any (other) children. This depended partly on their subjective assessment of the transmission risk. Others felt that they did not know what the side effects and the outcome of using these techniques would likely be. One interviewee also reflected that she would not want to be the first person to 'experiment' using MRTs, even though she was ready to use PGD: 'The advantage of PGD is that it's tried and tested. PGD is happening every single day for loads of different conditions so I do like to know that there are more certainties than uncertainties and with PGD. [Mitochondrial donation] has never been done before on a real baby'.

⁵¹ S. Franklin & C. Roberts. 2006. *Born and Made: An Ethnography of Preimplantation Genetic Diagnosis*. Princeton and Oxford: Princeton University Press, 2006; C. Dekeuwer & S. Bateman. Much More than a Gene: Hereditary Breast and Ovarian Cancer, Reproductive Choices and Family Life. *Medicine, Health Care and Philosophy* 2011; 16: 231–44; U. Menon et al. Views of BRCA Gene Mutation Carriers on Preimplantation Genetic Diagnosis as a Reproductive Option for Hereditary Breast and Ovarian Cancer. *Human Reproduction (Oxford, England)* 2007; 22: 1573–77.

Several women also disapproved of or would not want to use MRTs because of religious or ethical reasons. These are some of the reasons why, in such circumstances, several participants preferred to use another available reproductive option, such as adoption, egg donation, prenatal testing or PGD⁵². However, these options were rarely mentioned during the public and parliamentary debates, reflecting the way the debates have contributed to valuing and strengthening biological kinship: it was implicit that there was a need to have a biological child and that this need should be fulfilled whatever the circumstances.

It is important to note that it is not because these women were not willing to use the techniques personally that they were against the legalisation of MRTs. This echoes findings of research into the attitudes of carriers of inherited breast cancer, which has shown that while the majority of participants considered that PGD should be an available option, they were divided over the possibility of using it personally⁵³. This also highlights the considerable divergence that can exist between people's public and private views on sensitive topics, i.e. they might have private convictions that diverge from the policy they want or have to defend in the public sphere⁵⁴.

4. Who will be able to afford MRTs?

The issues of the cost and the financing of MRTs were rarely discussed during the debates. In an annex of the consultative document on draft regulations published by the Department of Health, there was a mention of an estimation of the cost that indicated: 'each cycle of mitochondrial donation treatment will use resources equivalent to two "rounds" of standard IVF (due to the need for a donor mother and the birth mother to have their eggs extracted), [plus] one round of Pre-implantation Genetic Diagnosis (PGD) to test for the presence of mitochondrial disease in the extracted embryos. [...] Using current costs, we estimate each cycle of mitochondrial donation should cost in the region of £20,000'⁵⁵. However, a successful conception is expected to require four cycles, as the success rate is estimated to be 25% per cycle. In this case, this means that the estimated cost of successful mitochondrial donation treatment, i.e. that resulting in a birth, if future intending mothers do not present any fertility problems, would therefore be approximately £80,000. This will of course vary according to the provider and to the efficiency⁵⁶ of the treatment.

In such circumstances, one might wonder how many people will be able to afford MRTs if they are not funded by the NHS.

To put this into perspective, it is worth mentioning that amongst my research participants, three couples who had previously lost a child affected by mitochondrial disorders had to give up on PGD because they thought it was too expensive (£7,000-13,000 per cycle). PGD is funded by the NHS only under specific circumstances. Funding is not available if, for instance, the couple or one of the intending parents already had a previous healthy child,

⁵² Participants' initial views on technology may nonetheless change and thus cannot be regarded as predictive.

⁵³ U. Menon et al. *op. cit.* note 51, p. 1573–7.

⁵⁴ K. Ehrich, C. Williams & B. Farsides. The embryo as moral work object: PGD/IVF staff views and experiences. *Sociol Health Illn.* Jul 2008;30(5):772–87.

⁵⁵ Department of Health, *op. cit.* note 38, p. 38.

⁵⁶ In this respect, it is worth mentioning that only two babies have been conceived and born in the UK using PGD for mitochondrial disorders at the time of the publication of this paper.

which was the case for these three couples. While the possibility for MRTs to be publically funded is currently under discussion with the NHS⁵⁷, one can wonder whether the conditions for PGD will apply to MRTs, and if this is the case, whether it would be a good time to adjust these rules in order to facilitate reproductive choices for intending parents. More generally, it is regrettable that the financial aspects of MRTs, the funding of which is considerable, have not been addressed in more depth during the public debates. In a context of limited health care resources, it could have been worth assessing and discussing the cost/effectiveness of MRTs with respect to other treatments already available or under development.

Conclusion

The considerations outlined above shed a different light on the discourses and the assumptions that have dominated the public domain in the UK in relation to MRTs. Drawing on insights gained from empirical data collected with women affected by the condition and on the analysis of various public documents, the paper puts into perspective the scope of MRTs and the potential number of targeted women. The discussion in this paper does not suggest that these techniques are not of value, and that their legalisation and their use should be resisted, or that they will not contribute to helping several families to have healthy children. However, analysis demonstrates that there is an important gap between the ways these techniques have been presented in the media and in the public domain, i.e. often as a kind of ‘miracle solution’ that will eradicate the disorders, and the social and medical constraints surrounding their use. In particular, the distinction between mitochondrial disorders produced by mutations in mitochondrial DNA and those produced by nuclear defects, along with their relative implications, has disappeared in the debates.

In addition, this paper shows that contrary to their representations in the media and in public discourse, families affected by mitochondrial disorders are very diverse and each faces specific issues in terms of quality of life and reproductive choices. It is important to consider and understand all family situations, in particular those who still do not have access to reproductive technologies, and to provide policy-makers and stakeholders with detailed information on their needs in order to support these families adequately. This is especially important in the longer term, if we do not want these debates to disseminate a narrow and misleading vision of the situation faced by individuals affected by mitochondrial disorders and to give the impression that reproductive issues for these families are now resolved.

Besides ethical and safety issues, it is therefore crucial to provide the public and policy-makers not only with accurate and relevant information on the techniques and the medical conditions discussed, but also with empirical analysis of existing situations and to situate them within their broader context. Adopting a sociologically-based approach is indeed also ‘necessary and integral to the bioethical process as a whole’⁵⁸. It is essential for understanding the complex mix of hopes, ambivalences and uncertainties that new biotechnologies can generate and their broader implications for societies.

⁵⁷ D. Turnbull. Why do we need mitochondrial donation. Presentation at the Annual Conference of the Progress Educational Trust, 9 Dec. 2016.

⁵⁸ S. Chan. A Bioethics for All Seasons. *Journal of Medical Ethics* 2015; 41: 19.

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